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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCESOPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361MEMORANDUM

DATE: 4/30/02

SUBJECT: **Iprovalicarb.** Chronic and Cancer Dietary Exposure Assessment for the Use on Imported Grapes.

DP Barcode:	D282211	PRAT Case:	292131
Submission No.:	S605880	Caswell No.:	NA
Chemical No.:	098359	Class:	Fungicide
Trade Name:	Melody WG50	EPA Reg No.:	NA
40 CFR:	NA	MRID No.	None

FROM: William D. Cutchin, Chemist *William D. Cutchin*
Science Information Management Branch
Health Effects Division (7509C)THRU: Richard A. Loranger, Branch Senior Scientist *R. Loranger*
Registration Action Branch 2
Health Effects Division (7509C)

and

Chemistry Science Advisory Council (Chem SAC)
Health Effects Division (7509C)

and

Christina Swartz *Christina Swartz*
Leung Cheng *Leung Cheng*
Dietary Exposure Science Advisory Council (DESAC)
Health Effects Division (7509C)TO: Richard Keigwin
Fungicide Branch
Registration Division (7505C)

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EPA Reviewer: William Cutchin, Date 4/9/02

STUDY TYPE: Iprovalicarb Chronic and Cancer Dietary Exposure Assessments for the use on Imported Grapes.

ACTIVE INGREDIENT: iprovalicarb

SYNONYMS: none

RESIDUE OF CONCERN: iprovalicarb *per se* [2-methyl-1[[[(1S)-(4-methylphenyl)ethyl]amino]carbonyl]propyl]carbamic acid methylethylester]

Executive Summary

The chronic and cancer dietary exposure assessment was requested to determine the dietary exposure estimates associated with the use of the fungicide iprovalicarb in/on grapes to support the request, PP#9E06020. Tolerances are proposed on grapes at 2.0 ppm. The request is for a tolerance without a U.S. registration. This is the first dietary exposure analysis for iprovalicarb.

Unrefined, Tier 1, chronic and cancer dietary risk assessments were conducted for the proposed iprovalicarb food use. Dietary risk estimates are provided for the general U.S. population and various population subgroups. This assessment concludes that for all included commodities, the chronic risk estimates are below the Agency's level of concern (<100% cPAD) for the general U.S. population (2.6% of the cPAD) and all other population subgroups. The chronic dietary exposure estimate for the most highly exposed population subgroup, children 1-6 years old, is 9.3% of the cPAD. The cancer dietary exposure estimate associated with the use of iprovalicarb for the general U.S. population is 3.10×10^{-7} , and is below the Agency's level of concern (1.0×10^{-6}). An acute dietary exposure estimate is not required for iprovalicarb.

I. Introduction

Risk assessment incorporates both exposure and toxicity of a given pesticide. The risk is expressed as a percentage of a dose that could be expressed as a daily or a long term dose, to pose no unreasonable adverse effects. This is called the population adjusted dose (PAD), and is expressed as %PAD. References are available on the EPA/pesticides web site which discuss the acute and chronic risk assessments in more detail: "Available Information on Assessing Exposure from Pesticides, A User's Guide", 6/21/2000, web link: <http://www.epa.gov/fedrgstr/EPA-PEST/2000/July/Day-12/6061.pdf>; or see SOP 99.6, 8/20/99.

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The purpose of this memorandum is to summarize the results of the dietary risk assessment for the general U.S. population and various population subgroups resulting from exposure to iprovalicarb through food. This is the first dietary risk analysis conducted for iprovalicarb.

II. Toxicological Information

The HIARC evaluated the toxicological data and established endpoints for iprovalicarb (HIARC, 1/22/02). The HED Cancer Assessment Review Committee (CARC, 2/21/02) has classified iprovalicarb into the category "Likely to be carcinogenic to humans." The most potent unit risk, Q_1^* (mg/kg/day)⁻¹, for iprovalicarb was determined to be 4.5×10^{-4} . The endpoints are summarized in Table 1. The FQPA Safety Factor Committee reduced the iprovalicarb FQPA safety factor to 1X for chronic exposure (FQPA, 3/11/02).

Table 1. Summary of Toxicological Dose and Endpoints for Iprovalicarb for Use in Dietary Exposure Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT/STUDY	RATIONALE
Acute Dietary (General Population including Infants & Children)	5000	LOAEL = limit test dose (>5000 mg/kg)	Iprovalicarb was of low acute oral toxicity in rats with no effects observed at doses well above the limit test dose (>5000 mg/kg). In addition, rat and rabbit teratology studies and an acute neurotoxicity rat study, presented no effects indicative of early toxicity. Also, in sub-chronic feeding and reproduction toxicity studies, there were no treatment related effect that could be attributable to a single dose.
	U.F. = NA		
	No acute endpoint established.		
Chronic Dietary	NOAEL = 2.62	The NOAEL of 2.62 mg/kg bw/day from a 1-year dog study	Based on liver effects (swelling, enlargement, distinct lobulation and discolouration, increased absolute and relative liver weights, and accompanying hepatocellular hypertrophy and fatty change, and elevated serum liver enzyme activities) (LOAEL 25 mg/kg bw/day).

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EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT/STUDY	RATIONALE
	U.F. = 100 FQPA = 1X	Chronic RfD = 0.0262 mg/kg/day	Chronic PAD = 0.0262 mg/kg/day
Cancer Classification and Method of Quantification			
Classification	Likely to be carcinogenic to humans		
Basis for Classification	This classification is based on combined follicular cell adenomas and carcinomas in the thyroid gland of female rats.		
Method of Quantification(RfD, MOE, Q ₁ *)	$Q_1^* \text{ (mg/kg/day)}^{-1} = 4.5 \times 10^{-4}$		

III. Residue Information

Chronic Assessment:

No tolerances for iprovalicarb have yet been established. A tolerance is proposed for residues on grapes at 2.0 ppm.

Percent Crop Treated Information:

For this analysis, proposed tolerance level residues and 100 percent crop treated assumptions were made for all grape commodities.

Processing Information:

Data from a grape processing study indicated that iprovalicarb residues did not concentrate in grape processed commodities. Therefore, DEEM™ concentration factors were set to 1 for this analysis.

Residue Estimates:

For this analysis, proposed tolerance level residues were used for all grape commodities. Additional refinements using anticipated residues would further refine this estimate.

IV. DEEM™ Program and Consumption Information

The iprovalicarb chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.76, which incorporates

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consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire US population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups from the general U.S. population which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

V. Results/Discussion/Conclusions

HED's level of concern is 100% of the PAD. That is, estimated exposures above this level are of concern, while estimated exposures at or below this level are not of concern. The DEEM analyses estimate the dietary exposure of the U.S. population and 26 population subgroups. The results reported in Table 2 are for the U.S. Population (total), all infants (<1 year old), children 1-6, children 7-12, females 13-50, males 13-19, males 20+, and seniors 55+.

Chronic Dietary Exposure Analysis

The Tier 1 chronic dietary risk assessment was conducted for the proposed iprovalicarb food uses. Dietary risk estimates are provided for the general U.S. population and various population subgroups. This assessment concludes that for all included commodities, the chronic risk estimates are below the Agency's level of concern (<100% cPAD) for the general U.S. population (2.6% of the cPAD) and all other population subgroups. The chronic dietary exposure estimate for the most highly exposed population subgroup, children 1-6 years old, is 9.3% of the cPAD.

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Cancer Dietary Exposure Analysis

HED's level of concern for cancer exposure is 1×10^{-6} . The lifetime risk of developing cancer from iprovalicarb exposure is determined for the U.S. population (total) only. The estimated exposure to iprovalicarb is 0.000688 mg/kg/day. Applying the Q_1^* of 4.5×10^{-4} (mg/kg/day) $^{-1}$ to the exposure value results in a cancer risk estimate of 3.10×10^{-7} . Therefore, the lifetime cancer risk to the U.S. population is below HED's level of concern.

VI. Discussion of Uncertainties

For this analysis, tolerance level residues and 100 percent crop treated assumptions were used for all grape commodities. Additional refinements using anticipated residues and percent crop treated data would further refine this estimate. DEEM™ concentration factors were set to 1 for this analysis.

Table 2. Summary of Dietary Exposure and Risk for Iprovalicarb

Population Subgroup**	Acute Dietary		Chronic Dietary		Cancer
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Risk or MOE
U.S. Population (total)	NA		0.000688	2.6	3.10×10^{-7}
All Infants (< 1 year)			0.001282	4.9	NA
Children 1-6 years			0.002443	9.3	
Children 7-12 years			0.000668	2.6	
Females 13-50			0.000537	2.0	
Males 13-19			0.000249	1.0	
Males 20+ years			0.000431	1.6	
Seniors 55+			0.000497	1.9	

VII. List of Attachments

Attachment 1 Dietary Exposure Input File
Attachment 2 Chronic Dietary Exposure File
Attachment 3 Cancer Dietary Exposure File

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Attachment 1

Filename: E:\working\iproval\098359.RS7 Chemical: Iprovalicarb
RfD(Chronic): .0262 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day Q* = .00045
Date created/last modified: 04-04-2002/10:29:04/8 Program ver. 7.76

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj. Factors #1	Adj. Factors #2	Comment
13	0	Grapes	2.000000	1.000	1.000	
15	0	Grapes-juice	2.000000	1.000	1.000	
392	0	Grapes-juice-concentrate	2.000000	1.000	1.000	
195	0	Grapes-leaves	2.000000	1.000	1.000	
14	0	Grapes-raisins	2.000000	1.000	1.000	
315	0	Grapes-wine and sherry	2.000000	1.000	1.000	

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Attachment 2

U.S. Environmental Protection Agency Ver. 7.76
 DEEM Chronic analysis for IPROVALICARB (1989-92 data)
 Residue file name: E:\working\iproval\098359.RS7 Adjustment factor #2 NOT used.
 Analysis Date 04-04-2002/11:01:23 Residue file dated: 04-04-2002/11:00:16/8
 Reference dose (RfD, Chronic) = .0262 mg/kg bw/day

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Total exposure by population subgroup

Population Subgroup	Total Exposure	
	mg/kg body wt/day	Percent of Rfd
U.S. Population (total)	0.000688	2.6%
U.S. Population (spring season)	0.000558	2.1%
U.S. Population (summer season)	0.000795	3.0%
U.S. Population (autumn season)	0.000901	3.4%
U.S. Population (winter season)	0.000474	1.8%
Northeast region	0.000694	2.6%
Midwest region	0.000639	2.4%
Southern region	0.000499	1.9%
Western region	0.001063	4.1%
Hispanics	0.000530	2.0%
Non-hispanic whites	0.000723	2.8%
Non-hispanic blacks	0.000590	2.3%
Non-hisp/non-white/non-black	0.000614	2.3%
All infants (< 1 year)	0.001282	4.9%
Nursing infants	0.001866	7.1%
Non-nursing infants	0.001036	4.0%
Children 1-6 yrs	0.002443	9.3%
Children 7-12 yrs	0.000668	2.6%
Females 13-19 (not preg or nursing)	0.000280	1.1%
Females 20+ (not preg or nursing)	0.000549	2.1%
Females 13-50 yrs	0.000537	2.0%
Females 13+ (preg/not nursing)	0.000248	0.9%
Females 13+ (nursing)	0.001238	4.7%
Males 13-19 yrs	0.000249	1.0%
Males 20+ yrs	0.000431	1.6%
Seniors 55+	0.000497	1.9%
Pacific Region	0.001267	4.8%

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Attachment 3

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U.S. Environmental Protection Agency
DEEM Chronic analysis for IPROVALICARB
Residue file name: E:\working\iproval\098359.RS7 Adjustment factor #2 NOT used.
Analysis Date 04-04-2002/11:01:36 Residue file dated: 04-04-2002/11:00:16/8
q* = 0.00045

Ver. 7.76

(1989-92 data)

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Total exposure by population subgroup

Population Subgroup	Total Exposure	
	mg/kg body wt/day	Lifetime risk (q* = .00045)
U.S. Population (total)	0.000688	3.10E-07